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EDITORIAL

Taking care of the caretakers to enhance antiretroviral adherence in HIV-infected children and adolescents☆,☆☆

Cuidando dos cuidadores para melhorar a adesão antirretroviral em crianças e adolescentes infectados com o HIV

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The article by Cruz et al., ''Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study,''[1] published in this journal reports important results regarding adherence to combined antiretroviral treatments from a large multicenter trial in perinatal human immunodeficiency virus (HIV)-infected children and adolescents with HIV in five geographically-distinct reference centers of Brazil. Although major advances have been made in the diagnosis, treatment, and access to antiviral drugs for children and adolescents with HIV, the desired outcome of a healthy and prolonged life is limited by the ability of the child/adolescent and the caregiver to consistently adhere to the daily need to take multiple antiretroviral medications.[2] Chronic administration of medication is a considerable challenge in most populations, and especially so in adolescents.[3]

As reported by Cruz et al., despite collection of data from questionnaires with adherence rates of 92.6% of children (caregivers information) and 77.2% of adolescents, only 57% of children and 28/57 (49%) of adolescents had documented HIV RNA viral loads below 50 cp/mL. Adherence to medications is critical to assure persistent suppression of HIV to undetectable levels, which allows for the potential reconstitution of CD4 T-cells and immune competence, preventing the rapid development of antiviral resistance and ultimate virological failure. There are limited opportunities for new effective antiviral regimens, as observed in this population, where 63% of subjects were on or beyond their second regimen. Our goals should be directed towards improving medication adherence with the first regimen, given to children and adolescents as early as possible following diagnosis in order to maximize the long-term outcome and reduce the potential for development of viral drug resistance.

Numerous studies have used different methods to assess adherence in HIV-infected children and adults with varying results. In pediatric populations, adherence questionnaires about cART-missed doses are used most frequently as in adults. Other methods include records of pharmacy visits; medication diaries; pill counts by study personnel and by electronic devices such as Medication Event Monitoring System (MEMS) (AARDEX Ltd, Union City, CA, USA)

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caps; and therapeutic drug monitoring.[4–6] The article by Cruz et al. found that the questionnaires about adherence were unreliable, since the caretakers and adolescent subjects were more optimistic about the consistency of adherence than what was evidenced by the percentage of children/adolescents with documentation of controlled viral replication. Several key points are worthy of reiteration; if instituted, they could improve the overall outcome of HIV-infected children and adolescents.

The authors observed that careful monitoring of pharmacy records are key to assure adherence, since those who returned approximately monthly for new prescriptions were significantly more likely to remain virologically suppressed than those who came less frequently. There ought to be a monthly flag sent to clinicians and care partners if prescriptions are not picked up. Other innovative solutions, such as home delivery of medications, could be used if necessary. Pharmacy reports can provide immediately useful information that can be easily incorporated into routine care as a monitoring tool.[7]

Another key component was the finding that health; use of drugs and alcohol; and mental, cognitive, and quality of life assessments of the caregiver were very important in predicting adherence and in identifying areas to provide assistance. The authors used the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) as a screening tool for caretakers; this practice has been proven successful in other studies and is recommended by the World Health Organization (WHO) for adults with HIV, since management of substance abuse has been associated with commitment to cART treatment 28.

As expected, a negative association between moderate/heavy alcohol consumption and viral suppression has been reported in the literature.[8] Likewise, increased anxiety scores of caretakers have been associated with poor adherence. In such cases, focused interventions to help the caretakers could then be instituted. The incorporation of a screening instrument for drug use and quality of life among caregivers may contribute to strategies aiming to improve adherence in the pediatric population.

During this study, from 2009 to 2011, the majority of children and adolescents in follow-up were diagnosed late, at a median of 9.5 years after the onset of symptoms, and 43% were diagnosed after the onset of acquired immunodeficiency syndrome (AIDS), which may reflect on the ability to achieve sustained viral suppression, as well as family attitudes about the necessity of daily ARV treatment. The best adherence rates were observed in infants or children diagnosed early as a result of follow-up of a HIV-seropositive mother or family member.

Advances in the integrated care of HIV-infected pregnant mothers and HIV-exposed children, availability of early diagnosis, better access to antiviral medications, and changes in ARV guidelines have greatly improved the initiation of cARV in pediatric and adolescent populations in Brazil and elsewhere.[9]

Due to a major reduction in early mortality and morbidity with initiation of early combined antiviral treatment in infants, treatment of all HIV-infected infants diagnosed less than one yearis now recommended.[10–12]

Improving the ability to sustain HIV viral suppression is a continuing challenge, not only to reduce the emergence of viral drug resistance and to improve the quality of life, but also to achieve the potential future goal of HIV remission.

A large clinical trial of prevention of mother-to-child HIV transmission conducted in Brazil, South Africa, Argentina, and the United States enrolled high risk infants within 48 hours of age, born to HIV-infected mothers who did not receive prenatal treatment, and showed that infants who received two or three ARVs prophylactically, compared to single dose Zidovudine, had 50% reduction of transmission at the time of birth.[13] This study observed that the identification of HIV-positive pregnant mothers at the time of delivery and their high-risk HIV-exposed neonates is feasible in Brazil and in other middle-income countries, such as South Africa; infants can be started on ARV very early as part of a comprehensive program of prevention of mother-to-child HIV transmission.

The recent report of HIV remission in an infant who was infected with HIV *in utero* and received early (31 hours of age) triple combination treatment, who has been off antiretroviral treatment for three years without evidence of HIV rebound, has spurred further studies of early ARV treatment for high-risk HIV infants and is expected to enroll in Brazil.[14,15]

In addition, recent studies in HIV-infected adolescents have shown that early combination treatment at less than 6 months of age and long-term, consistentlu tight control of viral replication in perinatally HIV-infected patients lead to reduction and continual decay of HIV viral reservoirs.[16–18] Improved point-of-care rapid diagnosis in infants and more frequent monitoring of HIV viral load in order to assure adequate viral suppression are still needed.

Starting combination ARV treatment early and assuring the best possible adherence during early years, with the goal of reducing HIV viral reservoirs and preserving immune function, and even preparing these children for strategies targeting HIV remission, is critical for their long-term outcome of these children.

These new goals make the findings of the article by Cruz et al. even more important, in order to direct efforts to enhance adherence in this vulnerable population, who depend on caretakers and medical infrastructure to ensure that medications are available and delivered over many years. We need to help take care of the caretakers of HIV infected children and adolescents.

Conflicts of interest

The author declares no conflicts of interest.

References

1. Cruz ML, Cardoso CA, Darmont MQ, Souza E, Andrade SD, D'Al Fabbro MM, et al. Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study. J Pediatr (Rio J). 2014;90:563–71.
2. Matida LH, Ramos Jr AN, Moncau JE, Marcopito LF, Marques HH, Succi RC, et al. AIDS by mother-to-child transmission: survival analysis of cases followed from 1983 to 2002 in different regions of Brazil. Cad Saude Publica. 2007;23:S435–44.
3. Marhefka SL, Koenig LJ, Allison S, Bachanas P, Bulterys M, Bettica L, et al. Family experiences with pediatric antiretroviral

therapy: responsibilities, barriers, and strategies for remembering medications. AIDS Patient Care STDS. 2008;22:637–47.
4. Kahana SY, Rohan J, Allison S, Frazier TW, Drotar D. A meta-analysis of adherence to antiretroviral therapy and virologic responses in HIV-infected children, adolescents, and young adults. AIDS Behav. 2013;17:41–60.
5. Williams PL, Storm D, Montepiedra G, Nichols S, Kammerer B, Sirois PA, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics. 2006;118:e1745–57.
6. Wachholz NI, Ferreira J. Adherence to antiretroviral therapy in children: a study of prevalence and associated factors. Cad Saude Publica. 2007;23:S424–34.
7. Ernesto AS, Lemos RM, Huehara MI, Morcillo AM, Dos Santos Vilela MM, Silva MT. Usefulness of pharmacy dispensing records in the evaluation of adherence to antiretroviral therapy in Brazilian children and adolescents. Braz J Infect Dis. 2012;16:315–20.
8. Rego SR, Rego DM. Association between the usage of alcohol by HIV patients and the adherence to the antiretroviral drug treatment: a literature review. J Bras Psiquiatr. 2010;59:70–3.
9. Wiegert K, Dinh TH, Mushavi A, Mugurungi O, Kilmarx PH. Integration of prevention of mother-to-child transmission of HIV (PMTCT) postpartum services with other HIV care and treatment services within the maternal and child health setting in Zimbabwe, 2012. PLoS One. 2014;9:e98236.
10. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008;359:2233–44.
11. Cotton MF, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, et al. Early time-limited antiretroviral therapy *versus* deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet. 2013;382:1555–63.
12. Nelson LJ, Beusenberg M, Habiyambere V, Shaffer N, Vitoria MA, Montero RG, et al. Adoption of national recommendations related to use of antiretroviral therapy before and shortly following the launch of the 2013 WHO consolidated guidelines. AIDS. 2014;28:S217–24.
13. Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012;366:2368–79.
14. Persaud D, Gay H, Ziemniak C, Chen YH, Piatak Jr M, Chun TW, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013;369:1828–35.
15. Hammer SM. Baby steps on the road to HIV eradication. N Engl J Med. 2013;369:1855–7.
16. Persaud D, Palumbo PE, Ziemniak C, Hughes MD, Alvero CG, Luzuriaga K, et al. Dynamics of the resting CD4(+) T-cell latent HIV reservoir in infants initiating HAART less than 6 months of age. AIDS. 2012;26:1483–90.
17. Luzuriaga K, Tabak B, Garber M, Chen YH, Ziemniak C, McManus MM, et al. HIV type 1 (HIV-1) proviral reservoirs decay continuously under sustained virologic control in HIV-1-infected children who received early treatment. J Infect Dis. 2014, pii: jiu297. [Epub ahead of print].
18. Buzon MJ, Martin-Gayo E, Pereyra F, Ouyang Z, Sun H, Li JZ, et al. Long-term antiretroviral treatment initiated in primary HIV-1 infection affects the size, composition and decay kinetics of the reservoir of HIV-1 infected CD4 T cells. J Virol. 2014, pii: JVI. 01046-14. [Epub ahead of print].